PCT

WORLD INTELLECTUAL PRO
International

INTERNATIONAL APPLICATION PUBLISHED UNDE

WO 9608468A1

(51) International Patent Classification 6 :
C07C 271/12, C07D 207/08, 211/22, 295/088, A61K 31/27, 31/40, 31/495

A1

(11) I

(43) International Publication Date: 21 March 1996 (21.03.96)

(21) International Application Number: PCT/DK95/00368

(22) International Filing Date: 14 September 1995 (14.09.95)

(30) Priority Data:
1056/94 14 September 1994 (14.09.94) DK

(71) Applicant (*for all designated States except US*): H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Valby Copenhagen (DK).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): FALCH, Erik [DK/DK]; Olgasvej 31, DK-2950 Vedbæk (DK). MIKKELSEN, Ivan [DK/DK]; Sankt Nikolaj Vej, 5 D, 1.th., DK-1953 Frederiksberg C (DK). KROGSGAARD-LARSEN, Povl [DK/DK]; Elmevej 25, DK-3450 Allerød (DK).

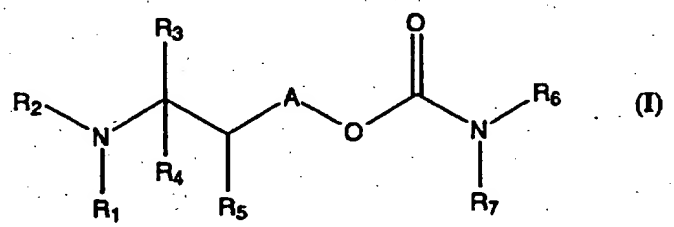
(74) Agent: MEIDAHL PETERSEN, John; H. Lundbeck A/S, Patent Dept., Ottiliavej 9, DK-2500 Valby Copenhagen (DK).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: CARBAMOYLOXY AMINE COMPOUNDS

(57) Abstract



(I)

Carbamoyloxypropylamine or carbamoyloxyethylamine compounds of formula (I), wherein A represents CH_2 or a bond, R_1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or phenyl; and R_2 is alkyl, alkenyl, alkynyl, cycloalkyl or phenyl; or R_1 and R_2 together form a ring; R_3 and R_4 are hydrogen, alkyl, alkenyl, alkynyl, halogenated alkyl, cycloalkyl, phenyl, or phenylalkyl or R_3 and R_4 together form a spirojoined C_{4-7} carbocycle; or when R_1 and R_2 are not linked, R_3 and R_2 may form ring; R_5 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, or phenylalkyl or together with R_2 form a ring; or R_5 together with R_4 form a ring; R_6 and R_7 are hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or phenylalkyl; or R_6 and R_7 together form a ring; are ligands at the central nicotine acetylcholine receptors (nAChRs). The compounds are useful in the treatment of cognitive, neurological or mental disorders in which nAChR dysfunction is involved.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

Carbamoyloxy Amine Compounds

The present invention relates to a novel class of carbamoyloxypropylamine or carbamoyloxyethylamine derivatives in which the alkyl backbone contains substituents or is partly incorporated into ring structures. The novel compounds are ligands at the central nicotine acetylcholine receptors (nAChRs) and accordingly useful in the treatment of certain cognitive, neurological and mental disorders.

Background of the invention

There is a rapidly growing interest in nAChRs in the central nervous system (CNS) as pharmacological and therapeutic targets (Williams et al., *Drug News & Perspectives* **1994**,*7*, 205-223.). There is convincing evidence of major impairments of central acetylcholine (ACh) neurotransmission in patients with Alzheimer's disease (Pomera et al., *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* **1986**,*10*, 553-569.; Perry, *Br. J. Psychiat* **1988**, *152*, 737-740.). Cortical nAChRs are markedly reduced in brain tissues from Alzheimer patients (Giacobini, *J. Neurosci Res.* **1990**, *27*, 548-560; Whitehouse et al., *Brain Res.* **1986**, *371*, 146-151), reflecting the cholinergic deficit associated with Alzheimer's disease. The parietotemporal cortex is the brain area which is most consistently implicated in the cognitive deficits in Alzheimer patients (Gitelman and Prohovnik,*Neurobiol. Aging.*, **1992** *13*, 313-318). Preclinical and clinical data are consistent with the view that nACh receptor agonists are useful in the treatment of Alzheimer's disease (Sahakian et al., *Br.J. Psych.* **1989**, *154*, 797-800; Levin, *Psychopharmacology* **1992** , *108*, 417-431).

In addition to its palliative effects on cognitive deficits in animal models and patients, nicotine, the most extensively studied nAChR ligand, also shows neuroprotective effects in models relevant to Parkinson's disease (Owman et al., *Prog. Brain Res.* **1989**, 79, 267-276; Williams et al., supra). Such observations make nACh receptors potential targets for therapeutic intervention in this neurologic disease (Aubert et al., *J. Neurochem.* **1992**, 58, 529-541). Similarly, nAChR ligands have therapeutic potential in schizophrenia (Adler et al.,*Biol. Psychiat.* **1992**, 32, 607-616). Furthermore, nicotine and other nAChR agonists have shown effects in animal models of anxiety (Brioni et al., *Eur.J. Pharmacol.* **1993**, *238*, 1-8) and pain

(Qian et al., *Eur. J. Pharmacol.* **1993**, *250*, 13-14; Badio and Daly, *Mol. Pharmacol.* **1994**, *45*, 563-569).

Tobacco smoke contains a variety of substances, but it is beyond doubt that the addictive nature of smoking is attributable to the content of nicotine. Consequently, nAChR ligands may be useful drugs in therapies for smoking cessation (for references, see Williams et al., supra).

Nicotine is the classical nACh receptor agonist, but the number of nACh receptor agonists and antagonists, synthesized or isolated from natural sources, is rapidly growing (Williams et al., supra).

A number of a analogues of carbamylcholine, including N-methylcarbamylcholine (MCC), (Boksa et al., *Eur. J. Pharmacol.* **1989**, *173*, 93-108; Abood et al.,*Pharmacol. Biochem. Behav.* **1988**, *30*, 403-408) and N,N-dimethylcarbamylcholine (DMCC) (Punzi et al., *Biochem. Pharmacol.* **1991**, *41*, 465-467; Sarawati et al.,*Drug Dev. Res.* **1994**, *31*, 142-146) have been synthesized and characterized as nAChR ligands. The compounds synthesized included some N-alkyl-, N,N-dialkyl and cycloalkyl carbamate estes of dimethylethanolamine and the N-methyl carbamate ester of dimethylpropanolamine.

Similar compounds are known from Chemical Abstracts **1961**, *55*, No CA p 6375a which discloses a few *N*-(dimethylcarbamoyloxyalkyl)dialkylamines, i.e. 3-dimethylcarbamoyloxy-*N,N*-dimethylpropylamine, 3-dimethylcarbamoyloxy-*N,N*-diethylpropylamine, 2-dimethylcarbamoyloxy-*N,N*-diethylpropylamine, 1-[3-(dimethylcarbamoyloxy)propyl]piperidine and 2-dimethylcarbamoyloxy-2-phenyl-1-methyl-*N,N*-dimethylethylamine. These compounds are claimed to exhibit choline esterase activity.

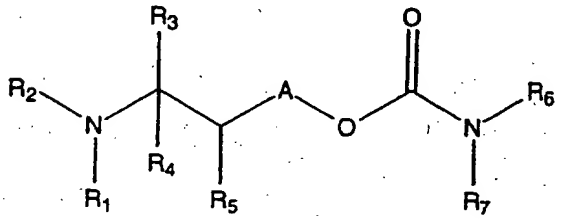
MCC appears to interact with presynaptically localized nAChRs involved in a positive feedback of ACh release (Araujo et al., supra; Lapchak et al., *J. Neurochem.* **1989**, *53*, 1843-1851). Within the compounds found to be nAChR ligands, the quaternary analogues, i.e. carbamate esters of choline, showed markedly higher nAChR affinity than the corresponding tertiary amines, i.e. carbamate esters of N,N-

dimethylaminoethanol (Abood et al., supra; Punzi et al., supra). Since the former group of analogues are likely to show a limited ability to penetrate the blood-brain barrier it is desired to obtain novel potent nAChR ligands having a good ability to penetrate the blood-brain barrier.

Summary of the invention

It has now been found that a series of novel tertiary amine homologues of DMCC are potent nAChR ligands.

Accordingly the present invention relates to a novel class of carbamoyloxy amine compounds of the formula I



FORMULA I

wherein A represents CH_2 or a bond,

R_1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or phenyl; and R_2 is alkyl, alkenyl, alkynyl, cycloalkyl or phenyl; or R_1 and R_2 together with the adjacent nitrogen form a 3 to 7 membered monoazacyclic ring;

R_3 and R_4 are the same or different and each represent hydrogen, alkyl, alkenyl, alkynyl, mono- or polyhalogenated lower alkyl, cycloalkyl, phenyl, or phenyl-lower alkyl or R_3 and R_4 together form a spirojoined C_{4-7} carbocycle; or when R_1 and R_2 are not linked, R_3 and R_2 may together with the nitrogen and carbon to which they are attached form a 3 to 7 membered monoazacyclic ring;

R_5 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, or phenyl-lower alkyl; or if R_2 do not form a ring with R_1 or R_3, then R_5 and R_2 may together with the nitrogen atom to which R_2 is attached, the carbon atom substituted with R_3 and R_4 and the carbon atom to which R_5 is attached, form a 3 to 7 membered monoazacyclic ring; or if R_3 is not included in a ring and R_5 do not form a ring together with R_2, R_5 and R_4 may together with the carbon atoms to which they are attached form a 3 to 7 membered carbocyclic ring; provided that R_5 is hydrogen when A is a bond;

R_6 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or phenyl-lower alkyl; and R_7 is alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or phenyl-lower alkyl, provided that R_7 cannot be phenyl or phenyl-lower alkyl when R_6 is hydrogen; or

R_6 and R_7 together with the adjacent nitrogen form a 5 to 6 membered monoazacyclic ring;

with the proviso that one of R_3 and R_4 must be different from hydrogen when A is a bond, R_1 is hydrogen or alkyl and R_2 is alkyl, and that R_3 and R_4 may not both be hydrogen when A represents CH_2, R_6 is hydrogen or methyl, R_7 is methyl and R_1 and R_2 are both alkyl or together with the N-atom to which they are attached form a piperidine ring;

and pharmaceutically acceptable salts thereof.

The compounds of the invention have been found to have a high affinity for nAChR's. Furthermore, some of the compounds have been found to exhibit nAChR agonist properties. Accordingly, the compounds of the invention are considered useful in the treatment of cognitive, neurological and mental disorders in which nAChR dysfunction is involved, such as pain, dementia, Alzheimers disease, Parkinsons disease, impaired learning ability, impaired memory function, psychosis, schizophrenia, pain and anxiety, in particular dementia, Alzheimers disease or impaired learning ability or memory function. Furthermore, they may be used in theraputical treatment for smoking cessation.

In another aspect the invention provides a pharmaceutical composition comprising at least one novel carbamoyloxy amine compound of formula I in a therapeutically effective amount.

In a further aspect the present invention provides the use of a carbamoyloxy amine compound of formula I for the manufacture of a pharmaceutical preparation for the treatment of the above mentioned disorders and diseases.

Detailed Description of th Inventi n

Some of the compounds of general Formula I may exist as optical isomers thereof and such optical isomers as well as any mixture thereof, including the racemic

mixtures, are also embraced by the invention.

In the present context, the term alkyl designates C_{1-8} alkyl which may be straight or branched such as methyl, ethyl, propyl, isopropyl, butyl, tert.butyl, pentyl, hexyl, heptyl or octyl. Among the alkyl groups, lower alkyl groups are preferred. The term lower alkyl designates C_{1-4} alkyl which may be a straight or branched such as methyl, ethyl, propyl, isopropyl, butyl, tert.butyl. Similarly, alkenyl and alkynyl, designate C_{2-8} groups having at least one double or tripple bond, respectively, and lower alkenyl and lower alkynyl designate such groups having up to 4 carbon atoms.

The term cycloalkyl designates a saturated carbocyclic ring having 3-7 carbon atoms, inclusive.

The term phenyl-lower alkyl designates a lower alkyl group (as herein defined) which, in turn, is substituted with a phenyl group. Preferred phenyl-lower alkyl are benzyl, 1-and 2-phenylethyl, 1-,2-, and 3-phenylpropyl, and 1-methyl-1-phenylethyl.

The term halogen designates F, Cl, Br or I, F being preferred. The term polyhalogenated lower alkyl designates lower alkyl, as defined above, substituted with two or more halogen atoms, which may be the same or different. A preferred example of polyhalogenated lower alkyl is trifluoromethyl.

The term a 3 to 7 membered monoazacyclic ring refers to a 3-, 4-, 5-, 6- or 7-membered ring containing one nitrogen atom, such as aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl or perhydroazepinyl. Preferred groups are pyrrolidinyl and piperidinyl.

The term 3 to 7 membered carbocyclic ring refers to a 3-, 4-, 5-, 6- or 7-membered carbon ring, for instance cyclopropane, cyclobutane, cyclopentane, cyclohexane or cycloheptane.

The salts of the compounds of the formula I include any pharmaceutically acceptable acid addition salt. This term as used herein generally includes the non-toxic acid addition salts of compounds of the formula I, formed with non-toxic inorganic or organic acids. For example, the salts include salts with non-toxic inorganic acids,

such as hydrochloric, hydrobromic, sulphuric, sulphamic, nitric, phosphoric and the like; and the salts with organic acids such as acetic, propionic, succinic, fumaric, maleic, tartaric, citric, glycolic, stearic, lactic, malic, pamoic, ascorbic, phenylacetic, glutamic, benzoic, salicylic, sulphonic, sulphanilic, and the like.

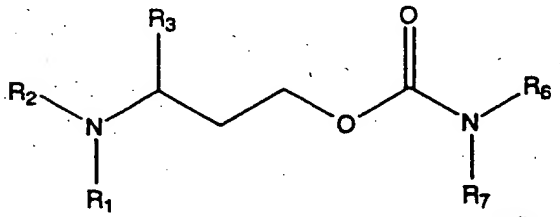
In formula I R_1 is preferably lower alkyl, most preferably methyl and R_2 is preferably lower alkyl, especially methyl, or designates together with R_3 and the nitrogen and carbon, repectively, to which R_2 and R_3 are attached a pyrrolidinyl ring or R_1 and R_2 may together form a pyrrolidinyl ring.

Furthermore, R_3 is preferably lower alkyl, or together with R_2 forms a ring, cf above. Most preferably R_3 is lower alkyl, especially methyl.

R_4 is preferably hydrogen and R_5 is preferably hydrogen or together with R_3 forms a ring, cf. above.

R_6 is preferably hydrogen or lower alkyl, most preferably hydrogen, ethyl or methyl and R_7 is preferably lower alkyl, most preferably ethyl or methyl.

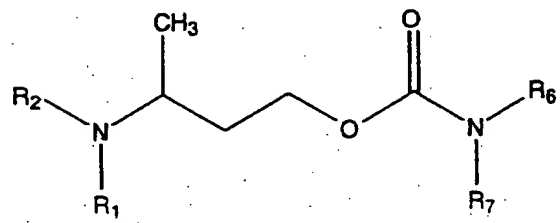
Preferred compounds of the invention are compounds of formula II



FORMULA II

wherein R_1, R_2, R_3, R_6 and R_7 are as defined above;

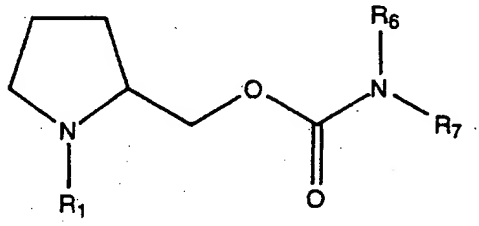
Especially preferred compounds of the invention are compounds of formula III



FORMULA III

wherein R_1, R_2, R_6 and R_7 are as defined above;

Another, subclass of preferred compounds of the invention are compounds of formula IV:



Formula IV

wherein R_1, R_6 and R_7 are as defined above.

Especially preferred compounds are:
(R,S)-4-Dimethylcarbamoyloxy-2-*N*,*N*-dimethylbutylamine
(S)-4-Dimethylcarbamoyloxy-2-*N*,*N*-dimethylbutylamine
(R)-4-Dimethylcarbamoyloxy-2-*N*,*N*-dimethylbutylamine

Compounds which may also be mentioned are:
4-Dipropylcarbamoyloxy-2-*N*,*N*-dimethylbutylamine
4-Ethylmethylcarbamoyloxy-2-*N*,*N*-dimethylbutylamine
4-Methylpropylcarbamoyloxy-2-*N*,*N*-dimethylbutylamine

The compounds of the invention are conveniently administered to a patient, via rectal, oral, parenteral or transdermal dosage forms or by inhalation as one or more daily doses, or other time-presented doses. The dose will, of course, depend on the requirements of the individual under treatment.

The effective daily dose of a typical compound is 5.0 µg to 1.5 mg, preferably 10 µg to 1.0 mg, in particular 25 µg to 0.5 mg pr. kg of body weight. Thus, the daily dose is generally in the range of 0.3 to 100 mg, preferably 0.6 to 60mg, usually 1.5 to 40 mg for typical compounds regardless of administration form. The daily dose may be administered in 1 to 3 single doses.

The compounds of the formula I may be administered in the form of tablets,

capsules, suspensions, emulsions, solutions, injectables, suppositories, enema, various drug delivery devices and in other suitable form. The route of administration may be rectally, orally, parenterally or transdermally or by inhalation. The formulation and preparation of any of these dosage forms is well-known to those skilled in the art of pharmaceutical formulation.

In a typical preparation for oral administration e.g. tablet or capsule, any one of the compounds of the present invention in a pharmacologically effective amount is combined with any oral nontoxic pharmaceutically acceptable inert carrier such as lactose, starch and microcrystalline cellulose. Additionally, when required, suitable binders (e.g. gelatin), lubricants (e.g. talc or magnesium stearate) and disintegrating agents (e.g. starch or various cellulose derivatives) are included.

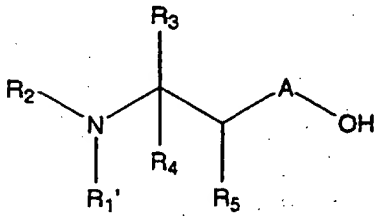
Similarly, in a typical formulation for parenteral application (intravenous, intramuscular, subcutaneous or the like), a compound of the present invention is dissolved in sterile water in a given concentration and sterilized by e.g. membrane filtration, or radiation. The pH of the solution may, if necessary, be adjusted with e.g. hydrochloric acid, sodium hydroxide or a suitable buffer, and a suitable preservative may optionally be added. Similarly, agents like sodium chloride may be added in order to adjust the tonicity of the solution. A suitable parenteral preparation may also consist of the compound formulated as a sterile, solid substance distributed in injection vials. Before dispensing, water for injection is added to dissolve the compound.

For the rectal application of the compounds of the invention, typical dosage forms include suppositories (emulsion and suspension types), rectal gelatin capsules (solutions and suspensions), and enemas or micro-enemas (solutions and suspensions). Thus, in a typical suppository formulation, a compound of the invention is combined with any pharmaceutically acceptable suppository base such as cocoa butter, esterified fatty acids (C_{10}-C_{18}), glycerinated gelatin, and various water-soluble or dispersible bases like polyethylene glycols and polyoxyethylene sorbitan fatty acid esters.Various additives like salicylates or surfactant materials may be incorporated. Enemas or micro-enemas of the solution type may simply be prepared by dissolving compounds of this invention in water or in water containing e.g. 0.5% of methylcellulose or another viscosity-increasing agent.

The novel and useful compounds of the invention may also be administered by drug delivery systems such as gastrointestinal drug delivery devices and rectally applied osmotic delivery devices, wherein the delivery device is manufactured from naturally occurring or synthetic polymeric materials.

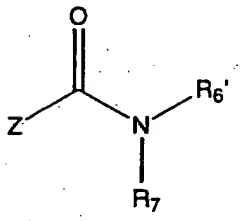
The compounds of the present invention may be prepared by :

a) Reacting a compound of the formula V



Formula V

wherein R_1' is as R_1 defined above or an amino protecting group, and R_2, R_3, R_4, R_5 and A are as defined above, with a compound of the formula VI

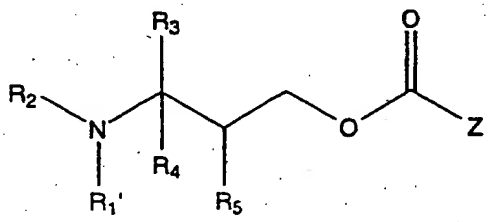


Formula VI

wherein R_6' is as defined above for R_6 except that it may not be hydrogen, R_7 is as defined above, and Z is a leaving group; and then, if an amino protecting group has been used, removing the said group;

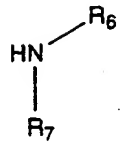
b) reacting a compound of the formula V as defined above with an isocyanate, R_7–N=C=O, wherein R_7 is as defined above and then, if an amino protecting group has been used; or

c) reacting a compound of the formula VII



Formula VII

wherein R_1', R_2, R_3, R_4, R_5, Z and n are as defined above, with a compound of the formula VIII



Formula VIII

wherein R_6 and R_7 are as defined above and then, if an amino protecting group has been used, removing the said group.

The reaction is carried out without a solvent or in a solvent, e.g. toluene, tetrahydrofuran, diethylether, acetonitrile, N,N-dimethylformamide (DMF), dimethyl sulfoxide, or the like. In a) and c) a base, e.g. sodium hydride, tertiary amine, pyridine, potassium carbonate, or the like, usually has to be present whereas in b) a base may be present if convenient. In a) and b) the temperature during the reaction is usually between 0°C and the boiling point of the mixture and in c) it is usually between -10°C and the boiling point of the mixture The reaction time is normally from 1 to 96 hours.

The compounds formulas V, VI and VIII are either commercially available or may be prepared by standard methods.

One way to obtain the compounds of formula VII may be by reacting a compound of formula V with phosgene.

Suitable leaving groups Z may easily be selected by a person skilled in the art. As examples may be mentioned chlorine, bromine and iodine.

The term amino protecting group designates groups readily removable by hydrolysis or hydrogenation. Suitable protecting groups may easily be selected. As examples of such groups may be mentioned methyloxycarbonyl, ethyloxycarbonyl, tert.butyloxycarbonyl, benzyloxycarbonyl, formyl, acetyl, trityl, benzyl, or the like.

The present invention is further illustrated by the following examples which, however, may not be construed to be limiting.

Example 1

(S)-2-Dimethylcarbamoyloxymethyl-1-methylpyrrolidine (Comp. (S)-**1**). Salt with 1.0 equivalent of tartaric acid

To a suspension of 80% sodium hydride dispersion (3.52 g; 117.4 mmol) in dry toluene (70 ml) was added a solution of (S)-2-hydroxymethyl-1-methylpyrrolidine (10.00 g; 87.0 mmol) in dry toluene (30 ml) over a period of 15 min. After 5 hours at 25°C, a solution of dimethylcarbamoyl chloride (11.20 g;104.4 mmol) in dry toluene (30 ml) was added over a period of 45 min., and the mixture was allowed to stir overnight at 25°C. Water (75 ml) was added, and the two phases were separated. The water phase was extracted with toluene (4 X 75 ml), and the combined organic phases dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude product (15.8 g) was purified by flash column chromatography on silica gel by use of triethylamine:toluene (1:20) and an increasing amount of ethyl acetate as eluent. The eluent was removed under reduced pressure and the purified product was obtained as a yellow oil (15.8 g; 98%). Part of the oil (1.40 g) was dissolved in dry isopropanol (5 ml) and a solution of L(+)-tartaric acid (1.24 g) in isopropanol (20 ml) was added followed by diethylether. After standing 72 hours at 5°C the title compound was isolated by filtration. Recrystallization from isopropanol and diethyl-ether gave the title compound (1.95 g; 77%), mp.: 82-84°C.

Example 2

(S)-2-Ethylcarbamoyloxymethyl-1-methylpyrrolidine (Comp. (S)-**2**). Salt with 1.0 equivalent of fumaric acid.

Ethyl isocyanate (1.23 ml; 15.7 mmol) was added to (S)-2-hydroxymethyl-1-methyl-pyrrolidine (1.50 g; 13.0 mmol) in dry toluene (10 ml) over a period of 5 min.. After 6 hours at 25°C another portion of ethylisocyanate (0.30 ml; 3.93 mmol) was added. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the crude product (2.22 g; 92%) was purified by flash column chroma-tography on silica gel by use of triethylamine:heptane (1:20) and an increasing amount of ethyl acetate as eluent. The eluent was evaporated under reduced pressure to give the free base of the title compound (1.96 g; 81%) as an oil. As described in Example 1, part of the oil (0.50 g) was converted to the fumaric acid salt by using fumaric acid. Recrystallization from isopropanol and diethylether gave

the title compound (0.63 g; 77%), mp.: 101.5-102.5°C.

Example 3

(R,S)-4-Dimethylcarbamoyloxy-2-*N,N*-dimethylbutylamine (Comp. **8**). Salt with 1.0 equivalent of fumaric acid.

(R,S)-3-*N,N*-Dimethylamino-1-butanol (4.29 g; 36.7 mmol) was added over a period of 10 min to a suspension of 60% sodium hydride dispersion (1.91 g; 47.7 mmol) in dry DMF (100 ml). After 3 hours at 40°C, dimethylcarbamoyl chloride (5.12 g; 47.7 mmol) was added over a period of 20 min. After another 4 hours at 40°C, the mixture was allowed to stir overnight at 25°C. After removal of the solvent under reduced pressure the residue was taken up in 100 ml water and extrated with diethylether (80 ml +3x30 ml). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure, leaving the crude product as a yellow oil (5.69 g; 83%). As described in Example 1, the oil was converted to the fumaric acid salt by using fumaric acid. Recrystallization from isopropanol and diethylether gave the title compound (5.78 g; 61%), mp.: 91-93.5°C.

Example 4

Cis-*N*-Methyl-2-dimethylcarbamoyloxymethylcyclopentylamine (Comp. cis-(1S,2R)-**18**). Salt with 1.0 equivalent fumaric acid.

Cis,trans-2-(*N*-benzyl-*N*-methylamino)cyclopentanemethanol (4.50 g; 18.4 mmol) was reacted with dimethylcarbamoyl chloride (2.67 g; 24.8 mmol) as described in Example 2. The crude product (5.55 g; 96%) was purified by flash column chromatography on silica gel by use of triethylamine:heptane (1:20) as eluent. The eluent was evaporated under reduced pressure and the *N*-benzylated title compound was obtained as an oil (1.85 g; 32%). Part of the oil (1.55 g; 5.34 mmol) was dissolved in acetic acid (50 ml) and hydrogenated with 120 mg prereduced PtO_2 at 3 atm.and 25°C for 24 hours. The solvent was removed under reduced pressure, and the crude product (1.09 g; 99%) was purified by flash column chromatography on silica gel by use of triethylamine:heptane (1:20) as eluent. The eluent was evaporated under reduced pressure to give the free base of the title compound (0.59 g; 54%) as an oil. As described in Example 1, the oil was converted to the fumaric acid salt. Recrystallization from isopropanol and diethylether gave the title compound (0.54 g; 80%), mp.: 102.5-103.5°C.

The following Table 1 lists further examples of the invention. The symbols used in the table refers to formula I. For the purpose of completion the compounds of Examples 1-4 are also included in the table.

The compounds were synthesized by methods analogeous to those described in Examples 1-4. Compounds (S)-8 and (R)-8 were prepared from Comp. 8 by standard resolution methods.

The following optical rotations have been measured, $[\alpha]_D^{25}$ deg.:

Comp. (S)-1: +3.7; Comp. (R)-1: -3.7; Comp. cis-(1S,2R)-18: -52.9; and Comp. cis-(1R,2S)-18: +52.7, Comp. (S)-8 (tartrate): -4.41, Comp. (R)-8 (tartrate): +4.97, (R)-30: +4.81 and (S)-30: 4.98.

Table 1: Examples

Comp.	A[1)]	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Mp °C (salt)[2)]
(S)-1	B	Me	$(CH_2)_3$		H	H	Me	Me	130.5-132.5 (T)
(R)-1	B	Me	$(CH_2)_3$		H	H	Me	Me	130-132 (B)
(S)-2	B	Me	$(CH_2)_3$		H	H	H	Et	101.5-102.5
(S)-3	B	Me	$(CH_2)_3$		H	H	Et	Et	102-103
(S)-4	B	Me	$(CH_2)_3$		H	H	H	Me	76-77.5
(S)-5	B	Et	$(CH_2)_3$		H	H	Me	Me	82-84
6	B	Me	$(CH_2)_4$		H	H	Me	Me	123-124.5
7	CH_2	Me	$(CH_2)_3$		H	H	Me	Me	95-96
8	CH_2	Me	Me	Me	H	H	Me	Me	91-93.5
(s)-8	CH_2	Me	Me	Me	H	H	Me	Me	120 dec. (DT)
(R)-8	CH_2	Me	Me	Me	H	H	Me	Me	120 dec. (DT)
9	CH_2	Me	Me	Et	H	H	Me	Me	102-103
10	CH_2	Me	Me	Me_2CH	H	H	Me	Me	96-100
11	CH_2	Me	Me	C_6H_{11}	H	H	Me	Me	130-133

Comp.	A*	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Mp °C
12	CH_2	Me	Me	$(CH_2)_5$		H	Me	Me	114-115
13	CH_2	H	Me	Me	H	H	Me	Me	66-68
14	CH_2	$(CH_2)_4$		Me	H	H	Me	Me	98-99
15	CH_2	$(CH_2)_5$		Me	H	H	Me	Me	121-125
16	CH_2	Me	Me	H	H	H	H	Et	84-87
17	CH_2	Me	Me	H	H	H	Et	Et	60-65
cis-18	CH_2	Me	Me	H	$(CH_2)_3$		Me	Me	126-127
trans-18	CH_2	Me	Me	H	$(CH_2)_3$		Me	Me	122-124.5
cis-(1S2R)18	CH_2	Me	Me	H	$(CH_2)_3$		Me	Me	146.5-167.5 (T)
cis-(1R,2S)18	CH_2	Me	Me	H	$(CH_2)_3$		Me	Me	146.5-167.5 (T)
19	CH_2	H	Me	H	$(CH_2)_3$		Me	Me	102.5-103.5
20	CH_2	Me	Me	H	$(CH_2)_4$		Me	Me	146-148
21	CH_2	$(CH_2)_4$		H	H	H	Me	Me	103.5-104.5
22	B	Me	Me	Me	Me	H	Me	Me	144.5-145.5
23	B	$(CH_2)_4$		H	H	H	Me	Me	110-113
24	B	$(CH_2)_4$		H	H	H	H	Et	62-64 (M)
25	B	$(CH_2)_5$		H	H	H	Me	Me	118-122
26	B	$(CH_2)_5$		H	H	H	H	Et	88-93
27	B	Me	Me	Me	H	H	Me	Me	112-117
28	CH_2	Me	R_2-R_5=$(CH_2)_2$;		R_3, R_4= H		Me	Me	84-85
29	CH_2	Me	R_2-R_5=$(CH_2)_3$;		R_3, R_4= H		Me	Me	112-113
30	CH_2	Me	Me	Me	H	H	H	Me	97-99
(R)-30	CH_2	Me	Me	Me	H	H	H	Me	91-91 (O)
(S)-30	CH_2	Me	Me	Me	H	H	H	Me	91-92 (O)
31	CH_2	Me	Me	Me	H	H	Et	Et	96-97.5 (C)

1): B designates a bond.

2): T designates tartrate, B hydrobromide, DT dibenzoyl tartrate; M maleate, O oxalate and C hydrochloride. The remaining compounds were isolated as fumarates.

Pharmacology

The compounds of the invention were tested in the following well recognized and reliable test methods.

L-[^{3}H]Nicotine binding

L-[^{3}H]Nicotine binding to cholinergic receptors in rat brain membranes was performed essentially as described by Lippiello, P.M. and Fernandes, K.G. *Mol. Pharmacol,* **1986**, *29*, 448-454.. Rat brains were homogenized (Ultraturrax) in 10 vol (w/v) buffer consisting of Na_2HPO_4, 8 mM; KH_2PO_4, 1.5 mM; KCl, 3 mM; NaCl, 120 mM; EDTA, 2 mM; HEPES, 20 mM; and iodoacetamide, 5mM (pH 7.4). The homogenate was centrifuged (50.000 x g; 20 min.; 0°C) and the pellet resuspended in 10 vol. cold standard assay buffer with the same composition as the buffer preparation described above, except for the addition of $MgCl_2$, 1mM and $CaCl_2$, 2 mM, and the elimination of EDTA and iodoacetamide. Aliquots (0.1 mg of tissue) were incubated with 5 nM L-[^{3}H]Nicotine (78 Ci/mmol, Amersham) alone or in the presence of test compound in a total volume of 0.6 ml for 60 min. at 0°C. Incubation was terminated by adding 5 ml of ice-cold sodium potassium phosphate buffer (50 mM, pH 7.4) followed by rapid filtration through Whatman GF/B filters presoaked in 0.1%polyethyleneimine using a Brandel cell-harvester. Filters were washed with three 5-ml aliquots of cold sodium potassium phosphate buffer, and bound radioactivity estimated by liquid scintillation counting methods. Each compound was tested in three different concentrations, and nonspecific binding estimated at 0.5 µM nicotine-H-tartrate. All estimations were made in triplicate, and each displacement experiment was repeated at least three times.

Table 2: L-[^{3}H] Nicotine Binding Data

Compound No	IC_{50}-values (μM) L-[^{3}H] Nicotine	Compound No	IC_{50}-values (μM) L-[^{3}H] Nicotine
1	0.068	cis-18	0.56
(S)-1	0.52	trans-18	2.3
(S)-2	0.66	cis-(1S,2R)-18	0.32
(S)-3	0.026	cis-(1R,2S)-18	0.65
(S)-4	0.30	19	5.4
(S)-5	0.59	20	27
6	11	21	1.8
7	1.6	22	67
8	0.009	23	0.63
(S)-8	0.064	24	2.2
(R)-8	0.003	25	11
9	0.15	26	47
10	2.9	27	2.3
11	80	28	6.0
12	29	29	47
13	1.6	30	0.008
14	33	(R)-30	0.006
16	0.64	(S)-30	0.39
17	0.84	31	0.014

Furthermore, the compounds of the invention have been tested with respect to affinity for muscarinic receptors by the method of Sauerberg, P. et al., *J. Med. Chem.* **1988**, *31*, 1312-1316, and some of compounds were tested with respect to agonistic effect at the nAChRs in the Guinea Pig Ileum test as described by Arnt et al. Eur. J. Pharmacol. **1992**, *218*, 159-169 or the Nicotine Cue test as described by L. T. Meltzer et al., Psychopharmacology 68, 283-286, 1980. Some of the compounds were selective towards the nAChRs as compared to muscarinic receptors whereas the compounds tested in the Guinea Pig Ileum test or the Nicotine Cue test were found to act as agonists.

Formulation Examples

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art as described above.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets containing 5.0 mg of active compound calculated as the free base:

Compound cis-(1S,2R)-18	5.0 mg
Lactose	60 mg
Maize starch	30 mg
Hydroxypropylcellulose	2.4 mg
Microcrystalline cellulose	19.2 mg
Croscarmellose Sodium Type A	2.4 mg
Magnesium stearate	0.84 mg

2) Tablets containing 10 mg of Compound 8 calculated as the free base:

Compound 8	10 mg
Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
Microcrystalline cellulose	14.4 mg
Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

3) Syrup containing per millilitre:

Compound (S)-1	25 mg
Sorbitol	500 mg
Hydroxypropylcellulose	15 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Flavour	0.05 mg

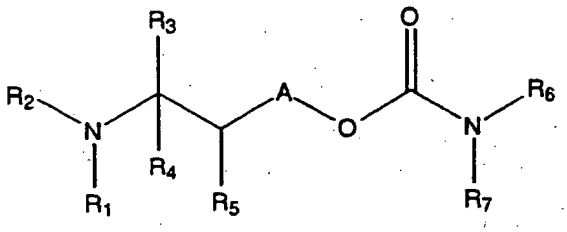
Saccharin natrium	0.5 mg
Water	ad 1 ml

4) Solution for injection containing per millilitre:

Compound **8**	20 mg
Sorbitol	5.1 mg
Acetic acid	0.08 mg
Water for injection	ad 1 ml

PATENT CLAIMS

1. A carbamoyloxypropylamine or carbamoyloxyethylamine compounds of the formula I



FORMULA I

wherein A represents CH_2 or a bond,

R_1 is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-7} cycloalkyl or phenyl; and R_2 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-7} cycloalkyl or phenyl; or R_1 and R_2 together with the adjacent nitrogen form a 3 to 7 membered monoazacyclic ring;

R_3 and R_4 are the same or different and each represent hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, mono- or polyhalogenated C_{1-4} alkyl, C_{3-7} cycloalkyl, phenyl, or phenyl-C_{1-4} alkyl or R_3 and R_4 together form a spirojoined C_{4-7} carbocycle; or when R_1 and R_2 are not linked, R_3 and R_2 may together with the nitrogen and carbon to which they are attached form a 3 to 7 membered monoazacyclic ring;

R_5 is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-7} cycloalkyl, phenyl, or phenyl-C_{1-4} alkyl; or

if R_2 do not form a ring with R_1 or R_3, then R_5 and R_2 may together with the nitrogen atom to which R_2 is attached, the carbon atom substituted with R_3 and R_4 and the carbon atom to which R_5 is attached, form a 3 to 7 membered monoazacyclic ring; or if R_3 is not included in a ring and R_5 do not form a ring together with R_2, R_5 and R_4 may together with the carbon atoms to which they are attached form a 3 to 7 membered carbocyclic ring; provided that R_5 is hydrogen when A is a bond;

R_6 is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-7} cycloalkyl, phenyl or phenyl-C_{1-4} alkyl; and R_7 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-7} cycloalkyl, phenyl or phenyl-C_{1-4} alkyl, provided that R_7 cannot be phenyl or phenyl-C_{1-4} alkyl when R_6 is hydrogen; or

R_6 and R_7 together with the adjacent nitrogen form a 5 to 6 membered monoazacyclic ring;

with the proviso that one of R_3 and R_4 must be different from hydrogen when A is a

bond, R_1 is hydrogen or C_{1-8} alkyl and R_2 is C_{1-8} alkyl, and that R_3 and R_4 may not both be hydrogen when A represents CH_2, R_6 is hydrogen or methyl, R_7 is methyl and R_1 and R_2 are both C_{1-8} alkyl or together with the N-atom to which they are attached form a piperidine ring;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim **1**, **characterized in** that R_1 and R_2 are both C_{1-4} alkyl, preferably methyl.

3. A compound of Claim **1**, **characterized in** that R_2 together with R_3 and the nitrogen and carbon, repectively, to which R_2 and R_3 are attached, designates a pyrrolidinyl ring.

4. A compound of Claim **1**, **characterized in** that R_1 and R_2 together with the nitrogen atom to which they are attached form a pyrrolidinyl ring.

5. A compound of Claim **1**, **characterized in** that R_3 is C_{1-4} alkyl, preferably methyl

6. A compound of Claim **1**, **characterized in** that R_4 together with R_5 and the carbon atoms to which they are attached form a cyclopentyl ring.

7. A compound of Claim **1**, **characterized in** that R_4 and R_5 are hydrogen.

8. A compound of any of Claims **1 - 7**, **characterized in** that R_6 is hydrogen or C_{1-4} alkyl, preferably hydrogen, ethyl or methyl and R_7 is C_{1-4} alkyl, preferably ethyl or methyl.

9. A compound of any of Claims **1 - 8**, **characterized in** that A is CH_2 and R_4 and R_5 are hydrogen.

10. A compound of Claims **9**, **characterized in** that R_3 is methyl.

11. A compound of Claim 1, **characterized in** that R_2 together with R_3 and the nitrogen and carbon, repectively, to which R_2 and R_3 are attached, designates a pyrrolidinyl ring, A represents a bond and R_4 and R_5 are hydrogen.

12. A compound of Claim 1, **characterized in** that it is selected from the group consisting of:
(S)-2-Dimethylcarbamoyloxymethyl-1-methylpyrrolidine,
4-Dimethylcarbamoyloxy-2-*N,N*-dimethylbutylamine,
(R,S)-4-Dimethylcarbamoyloxy-2-*N,N*-dimethylbutylamine,
(S)-4-Dimethylcarbamoyloxy-2-*N,N*-dimethylbutylamine,
(R)-4-Dimethylcarbamoyloxy-2-*N,N*-dimethylbutylamine and
Cis-*N*-Methyl-2-dimethylcarbamoyloxymethylcyclopentylamine; and
pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition, **characterized in** that it comprises at least one compound of any of Claims 1 - 12, in a therapeutically effective amount, together with one or more pharmaceutically acceptable carriers or diluents.

14. Use of a compound of any of Claims 1 - 12 for the manufacture of a pharmaceutical preparation for the treatment of a cognitive, neurological or mental disorders in which nAChR dysfunction is involved, preferably pain, dementia, Alzheimers disease, Parkinsons disease, impaired learning ability, impaired memory function, psychosis, schizophrenia, pain or anxiety or for theraputical treatment for smoking cessation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 95/00368

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 271/12, C07D 207/08, C07D 211/22, C07D 295/088, A61K 31/27, A61K 31/40, A61K 31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2704M A (SIEGFRIED, SOCIETE ANONYME RESIDANT EN SUISSE), 3 August 1964 (03.08.64) --	1-2,4-5, 7-10,13-14
X	CH 405266 A (SIEGFRIED AKTIENGESELLSCHAFT), 15 July 1966 (15.07.66) --	1-2,13-14
X	US 2794810 A (JOHN W. CUSIC), 4 June 1957 (04.06.57) --	1-2,4-5, 7-10,13
X	CH 467755 A (SIEGFRIED AKTIENGESELLSCHAFT), 14 March 1969 (14.03.69) --	1-2,4-5, 7-10,13

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" erlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1995	02 -01- 1996
Name and mailing address of the ISA/ Sw dish Patent Offic Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 95/00368

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 55, 25 December 1961 (25.12.61), (Columbus, Ohio, USA), THE ABSTRACT No 6375a, JP, 7464, A, (Dainippon Pharmaceutical Co., Ltd) 20 June 1961 (20.06.61) --	1-2,4-5, 7-10,13
X	CH 468978 A (SIEGFRIED AKTIENGESELLSCHAFT), 15 April 1969 (15.04.69) --	1-2,5,7,13
X	US 3347856 A (CARL D. LUNSFORD), 17 October 1967 (17.10.67) --	1,13-14
X	US 3287471 A (JOHN W. CUSIC ET AL), 22 November 1966 (22.11.66) --	1

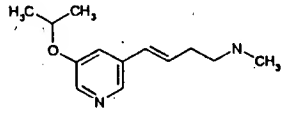
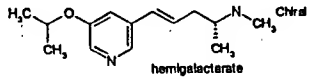
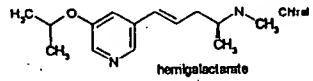
INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 95/00368

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A- 929707	03/08/64	NONE		
CH-A- 405266	15/07/66	NONE		
US-A- 2794810	04/06/57	NONE		
CH-A- 467755	14/03/69	DE-A-	1470277	29/05/69
JP-A- 7464	20/06/61	NONE		
CH-A- 468978	15/04/69	DE-A-	1470277	29/05/69
US-A- 3347856	17/10/67	BE-A-	676170	08/08/66
		CH-A-	467798	00/00/00
		FR-A-	1467524	00/00/00
		GB-A-	1136104	00/00/00
		LU-A-	50404	08/08/66
		NL-A-	6601380	09/08/66
		OA-A-	1912	04/02/70
		BE-A-	676256	16/06/66
		CH-A-	466282	00/00/00
		DE-A-	1620184	12/03/70
		FR-A-	1490497	00/00/00
		GB-A-	1128351	00/00/00
		NL-A-	6600234	10/08/66
US-A- 3287471	22/11/66	NONE		

Table 5

Compound	STRUCTURE	Ki	α4β2 Emax	α4β2 EC50	Activity Ratio Emax/EC50	Cp max (ng/mL)	AUC 0-∞ (h.ng/mL)
1		5	59	379	0.15	19	30
2	 hemigalacterate	62	14	88	0.16	28	50
3	 hemigalacterate	11	57	220	0.26	39	123